MIRECC

MENTAL ILLNESS RESEARCH, EDUCATION AND CLINICAL CENTER

Improving the long-term outcome of patients with serious mental disorders

MINDVIEW

Winter 2000

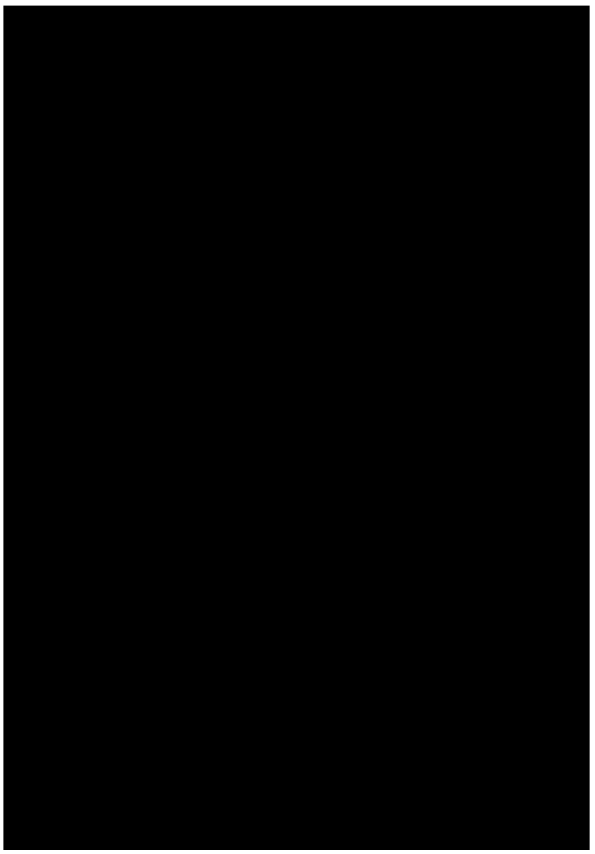
VA program studies brain activity

When Len Lulow arrives at La Jolla's Thornton Hospital to participate in research on brain function, he is first instructed to remove coins, jewelry and other metal objects that could harm magnetic equipment used in the study. He then enters a separate room containing magnetic resonance imaging (MRI) equipment, where he is given his assignment.

He will be asked to lie in the MRI chamber with his head in a square plastic helmet. A technician will attach a small mirror to the helmet, positioning it in front of Lulow's eyes. Reflected in the mirror, Lulow will see a yellow electronic "cursor" in the shape of a cross-hair, and above that, a laser-like red line that will move in a wave pattern from one side to the other. Inside the MRI chamber, Lulow will hold a rubber ball connected by plastic tubing to a pressure sensor. Lulow's task is to make the cursor follow the path of the red line by squeezing and releasing the ball.

Once the experiment gets under way, radiologists will make 20 scans or photographic "slices" of Lulow's brain, ensuring accuracy by repeating each scan 85 times for a total of 1,700 images. The task is somewhat like playing a videogame inside a million-dollar hollow tube while scientists monitor changes in brain activity.

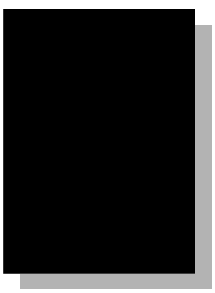
A VA research assistant with a master's degree in social work, Lulow is part of the study's "control" group of healthy individuals whose results will be compared to data from individuals with schizophrenia or bipolar disorder to gain a better understanding of brain malfunctions. This research is examining the function of left and right hemispheres of the basal ganglia,



Neuroscientist Mike Caligiuri (right) gives instructions to research assistant Len Lulow, who has volunteered to participate in a study on brain function.

Research could help improve psychiatric diagno-

Scientists at the Veterans' Affairs Healthcare System in southern California are conducting more than one dozen high-tech studies of the human brain in hopes of shedding new light on brain dysfunction associated with schizophrenia and other forms of mental illness. Their work could improve the diagnosis of mental disorders and enhance treatment monitoring.



Gregory Brown

Each of the research projects involves magnetic resonance imaging, a painless and safe technology that uses radio waves and a large magnet to create detailed black-and-white images of the brain. These particular studies take the MRI technology one step further by requiring research subjects perform various types of visual-motor tasks while technicians measure areas of brain blood flow, and therefore activation.

Differences in brain activation among "normal" and mentally ill individuals may reveal information crucial to understanding schizophrenia, bipolar disorder and other psychiatric illnesses. For example, the research on schizophrenia could lead to more precise diagnostic subcategories of the disease, more accurate predictions of patients' vocational success and new treatments

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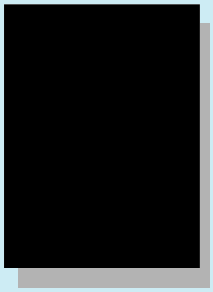
LETTER FROM THE DIRECTOR

MIRECC at forefront of brain



Steve Marder

The most important advances in scientific progress often follow from the discovery of new ways to look at the natural world. The discovery of the microscope or the telescope and access to the genetic code are examples of new ways to approach scientific question that resulted in enormous progress. This issue of the newsletter highlights MIRECC research that has benefited from advances in our ability to image the living brain.

The development of computerized methods for imaging the brain during the 1970s and 1980s led to rapid advances in our understanding of the relationships between abnormal anatomy and disease processes. Prior anatomical studies in schizophrenia relied on postmortem studies of the brain, and yeilded only ambiguous results. Studies using both computerized tomography (CT) and magnetic resonance imaging (MRI) have been more convincing. They provide compelling evidence that schizophrenia is associated with anatomical abnormalities.

Functional imaging methods including positron emission tomography (PET), MRI spectroscopy and functional MRI (fMRI) permit investigators to monitor the activity of the brain while the patient is carrying out a cognitive, sensory or motor task. The MIRECC has focused largely on fMRI, a method which measures changes in blood flow as a method for understanding changes in brain activity. These fMRI studies have found that individuals with schizophrenia process information differently than healthy individuals. The patients may exhibit a form of cognitive inefficiency that may explain the deficits in memory, attention and "executive function" common in schizophrenia. Understanding these deficits may permit investigators to explore pharmacological and rehabilitation strategies aimed at improving cognitive functioning.

We look forward to future improvements in patient care that may result

Technology may show nervous system basis of

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for neurological and cognitive difficulties, explained Gregory G. Brown, who has a doctorate in clinical psychology.

Historically, researchers viewed symptoms such as hallucinations and delusions as the primary problems for these patients. But newer research has pointed to fundamental shortcomings in memory, social interaction, judgment, planning and abstract thinking – all of which will be studied in the VA research, said Brown, who coordinates all psychiatric research using functional magnetic resonance imaging for the San Diego VA Healthcare System.

"In the last two decades, we have come to understand much more about neurological dysfunction in schizophrenia," he said. "Problems that patients with schizophrenia have with vocational and psychosocial success seem to be caused primarily by these underlying biological deficits in their thinking."

In other words, the difficulties that people with schizophrenia often experience in attempting to hold down jobs may result more from impaired memory, judgment and thinking than from hallucinations or delusions. Functional brain imaging aims to identify the nervous system basis of disordered thinking, memory and perception.

In one project, researchers are studying brain activation involved in the emotional responses of patients with schizophrenia. The experiments involve measuring areas of brain activity in patients with schizophrenia while they watch movies expected to evoke emotions such as hostility or anxiety. With the help of functional magnetic resonance imaging, or fMRI, the scientists may be able to pinpoint neurological malfunctions that cause these individuals to make inaccurate interpretations of others 'behavior.

In a different study, VA investigators are evaluating whether the anti-psychotic drugs Risperdal (resperidone) and Zyprexa (olanzapine) improve short-term visual memory. Research findings could lead to new memory-enhancing medications for mentally ill patients.

Other MIRECC-supported fMRI studies are evaluating the following:

- the effects of the Alzheimer's drug Aricept on memory in patients who take anti-psychotic drugs for schizophrenia;
- interaction of estrogen and Zyprexa in post-menopausal women with schizophrenia;
- brain function in people who are genetically at-risk for Alzheimer's disease;
- the results of alcohol dependence in young adults;
- neuron function in methamphetamine users;
- over-activity of certain brain regions among people with social phobia; and
- the effects of sleep deprivation on depression.

Functional magnetic resonance imaging has been used to study the brain for only about eight years. The technology may reveal insights not possible through any other research method.

"We're not there yet, but perhaps five years from now, we'll be able to use functional MRI to improve diagnosis and treatment monitoring of schizophrenia," Brown said. "Along the way, scientists also will learn more about the brain dysfunction associated with

Motor activities used to stimulate brain activity dur-

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Research Associate Boris Vukov demonstrates software and equipment used in research on brain activity among healthy and mentally ill subjects at the San Diego VA. When they squeeze and release the rubber ball, research subjects move the cursor on the computer monitor along the path of the wavy line. Brain activity tracked by MRI equipment during these experiments may help researchers better understand certain forms of mental illness.

a group of structures deep in the brain that are associated with schizophrenia and bipolar disorder. Psychiatric research has found malfunctions in the left side of the brain in schizophrenia and on the right side among people with bipolar disorder.

With the help of the sophisticated MRI technology, researchers may be able to determine whether the right and left sides of the basal ganglia respond differently in patients with schizophrenia and bipolar disorder. Such information could be key to understanding the root of pathology in these individuals.

In their initial studies, psychiatrist James Lohr and neuroscientist Mike Caligiuri found that when subjects traced a flat line, the basal ganglia did not become active. But when the line moved up and down in a wave pattern, requiring the subject to exert varying pressure on the rubber ball, the basal ganglia responded with increased blood flow and therefore, activity. The specific areas that became active were the basal ganglia on the same side of the brain as the hand that held the ball, and the motor, sensory and visual areas of the cortex, or outer layer of the brain.

The researchers now want to pinpoint whether the response from the basal ganglia was a result of visual or motor information. A study has been designed to elicit separate responses to visual and motor cues. To measure responses to visual cues, the electronic beam will at times move from right to left and at other times left to right. Requiring subjects to alternate between their right and left hands will give investigators information about activity in the brain's motor areas.

"It's not possible to separate the impact of visual and motor input without doing this kind of study," Caligiuri said. "To our knowledge, no other researchers have done this."

So far, only healthy individuals have participated in the study. In the future, data will be collected on individuals with schizophrenia and bipolar disorder. Comparing results of healthy individuals and people with schizophrenia and bipolar disorder may give the scientists a more precise understanding of the imbalance in the left and right sides of the brain, Caligiuri said. At present, researchers do not know whether the imbalance is a result of too much activity in these brain regions or too little.

"We want to know if one of the reasons patients have problems with hemisphere imbalance is because of over- or under-activation of one side of the brain or another, and we're using brain imaging to assess this," Caligiuri said.

Researchers will take additional measurements of the mentally ill patients when they experience an increase or decrease in symptoms and when their medication types or dosages are changed. These comparative measurements will tell researchers whether changes in symptoms are reflected in changes in brain activity. If so, this information eventually could lead to improvements in treatment. (Any changes in medication will be made for patient benefit only, not for research purposes. Also, all subjects are paid for their participation in research-related assessments and MRI sessions.)

Investigators also will compare test results of patients who are taking different prescribed anti-psychotic medications such as Seroquel (quetiapine fumarate), Risperdal (risperidone) and Zyprexa (olanzapine), which may reveal the effects of each of these drugs on the activity level of specific brain structures. For example, some studies have indicated a normalization of this asymmetry among patients taking Risperdal. Research could provide new information about which drugs are most effective at treating various symptoms of schizophrenia. The research results also could benefit individuals with bipolar disorder, as many of these individuals respond well to anti-psychotic medications, Lohr said.

About 70 percent of the funding for these studies comes from the National Institute of Mental Health. The VA's Mental Illness Research, Education and Clinical Centers, or MIRECC, contribute the other 30 percent.

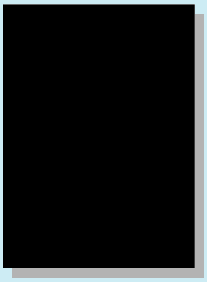
"With all of these projects, we hope to explain patients' hemispheric imbalances using functional imaging techniques and to draw more connections between the brain and behavior," Caligiuri said. "The more we learn through research, the more tools we eventually will have to help patients improve their day-to-day lives."

These research projects are funded in part by the Department of Veterans Affairs' Mental Illness Research, Education and Clinical Centers, or MIRECC. The Southern California MIRECC is one of eight VA programs established nationwide to improve the long-term functional outcome of mentally ill patients through research, clini-

THE FACES OF MIRECC

Once a young Jim Lohr set his career sites on science, the decision to study psychiatry came easily.

"I had always been interested in science, especially brain science, which is incredibly fascinating and complex," Lohr said. "Though I considered neurology and neurosurgery, I liked psychiatry better and found I enjoyed working with psychiatric patients."



James B. Lohr

In many ways, the field also offered nearly unlimited opportunities for learning, discovery and advancement of the field.

"I was intrigued by the possibilities of learning more about what goes on in the healthy brain as well as what goes wrong," he said.

After finishing medical school at the University of Chicago in 1980, Lohr completed his internship and residency in Pittsburgh, followed by a three-year neuropsychiatry fellowship at the National Institute of Mental Health. He now is vice chair for clinical affairs for the University of California at San Diego and chief of psychiatry for the VA San Diego Healthcare System, where his research includes using functional magnetic resonance imaging (fMRI) to study brain function in mentally ill individuals. Funded by the National Institute of Mental Health and the VA's Mentally Ill Research, Education and Clinical Center, or MIRECC, the studies use MRI equipment to monitor brain activity of research subjects as they complete various motor tasks.

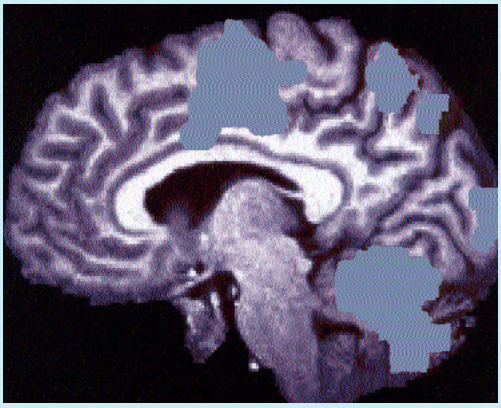
"We are using the motor system as a tool to study psychotic illness as a whole," Lohr said.

Comparative measurements of activity in the left and right hemispheres of the brains of mentally ill and healthy subjects give scientists a "window" through which to study psychosis and its effects, he explained. Many studies have found that schizophrenia, an illness involving impairment of a person's thinking abilities, shows greater abnormalities on the left side of the brain. Bipolar disorder, considered a disorder of emotions, appears to involve more of the brain's right hemisphere. Most research has viewed schizophrenia and bipolar disorder as two distinct illnesses. But this clear-cut distinction between these two disorders may have been faulty, Lohr speculated.

"One possibility we are investigating is whether schizophrenia and bipolar disorder actually have similar deep pathologies," Lohr said.

"The tendency to focus exclusively on one disorder or the other may be misguided," Lohr said. "Thinking and feeling are closely related, and on some level may even be the same."

By studying differences and similarities in brain function among patients with various disorders, Lohr and his research team may end up developing new ways of conceptualizing, and possibly treating, mental illness.



Scientists create brain scans like this during functional magnetic resonance imaging (MRI) studies. The shaded portions show areas of the brain that become active during various motor tasks.

"We may find a deeper underlying connection between psychotic disorders, which could shed light on treatment and drug development," Lohr said. "Our knowledge of these disorders could become synthesized into a more coherent understanding of mental functioning."

Born and raised in Chicago, Lohr originally planned to become a concert pianist. Though he still plays on occasion, he more often spends his free time with his grandchildren or cooking ethnic foods ranging from Greek to

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